Atty. Dkt. No. 092486-0102

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jens PETERSEN
Title:	**POLYACRYLAMIDE HYDROGEL FOR THE TREATMENT OF INCONTINENCE AND VESICOURETAL REFLUX**
Appl. No.:	09/938,667
Filing Date:	08/27/2001
Examiner:	Blessing M. Fubara
Art Unit:	1618
Confirmation No.	2505

DECLARATION OF ROBERT LESSÉL UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Robert Lessél, hereby declare as follows:

(1) I, Robert Lessél, am an expert in polymer chemistry ("the field"). My qualifications as an expert in the field are detailed in a curriculum vitae that is APPENDIX 1 to this Declaration.

(2) I provide consultation and know-how to Contura S.A. pursuant to an agreement on matters of process polymer chemistry. I am being compensated by Contura S.A. for my work regarding preparation of this declaration at my normal hourly rate. My compensation is not dependent on the substance of my opinions or on the disposition of this application.

(3) I previously submitted a declaration in connection with this application. For my work regarding the preparation of the earlier declaration, Contura S.A. compensated me for my work at my normal hourly rate. My compensation was not dependent on the substance of my opinions or on the disposition of this application.

(4) I have reviewed the pending claims of the subject application. Additionally, Applicant's representative to the PTO has informed me of certain issues that have arisen in the prosecution of the subject application.

(5) Accordingly, I understand the Examiner to be of the opinion that Vogel discloses a hydrogel and that this purported hydrogel renders obvious the "hydrogel" recited by the pending claims. Moreover, I understand that the Examiner is of the opinion that the complex viscosity and elastic modulus recited by the pending claims to be inherent in Vogel's microparticles. I respectfully disagree with these opinions, as I explain below.

(6) From a polymer chemistry perspective, Vogel's microparticles differ vastly from the hydrogel recited by the pending claims:

- Vogel discloses solid gel microparticles, which are far different from a "hydrogel"
- Vogel does not disclose or suggest "combining acrylamide and methylene bis-acrylamide"
- Vogel use a cationic polymer
- Vogel does not disclose microparticles comprising "about 0.5% to 25% by weight of a polymer," even if Vogel's microparticles could be considered a "hydrogel" and even if Vogel microparticles could be considered a polyacrylamide hydrogel
- Vogel does not disclose or suggest the recited molar ratios
- Vogel does not disclose or suggest a hydrogel with the recited rheological properties, as shown by the solid, rubber-like properties of the microparticles

I explain each of these differences and their significance in more detail below.

(7) As an initial matter, I disagree that Vogel discloses the use of a "hydrogel," as recited by the pending claims. Vogel generally discusses the use of "microparticles." Microparticles are far different from a "hydrogel." Vogel makes this distinction clear in Example 6.1 Specifically, Example 6.1 discusses making microparticles by forming a hydrogel, "cut[ting] [it] in small pieces," and then grinding the small pieces "to get very small particles." Thus, Vogel teaches that the hydrogel is cut and crushed to obtain the desired microparticles. This cutting and crushing would be extremely difficult, or impossible, with a polymer having a complex viscosity and elasticity modulus within the ranges recited by the claims.

(8) Microparticles are far different from a "hydrogel," however. Christensen *et al.*, AESTHETIC PLASTIC SURGERY 29: 34-48 (2005), nicely illustrates this distinction. Christensen states that there are "[t]here principally different filler types," including "a homogeneously built

polymer gel (silicone gel, polyacrylamide hydrogel)" and "[a] suspension of insoluble polymer or microspheres and a resorbable liquid" Christensen at p. 34, right column. The recited hydrogel is a "a homogeneously built polymer gel," and Vogel's microparticles fall into the latter category, a "suspension of insoluble polymer or microspheres." *See* Vogel at Example 6.1 (noting that the gel from which the microparticles were formed "was totally insoluble to water"). Christensen further highlights the distinction between homogeneously built polymer gels and microparticles by highlighting the distinctions between silicone gel and microparticulate silicone. Christensen at p. 35 (compare "Silicone Gel" section to "Polyvinylpyrrolidone-silicone Suspension" section). Accordingly, microparticles as taught by Vogel are not considered a "hydrogel," as claimed.

(9) Very real practical differences accompany the difference between microparticles and hydrogels. The different types of materials have significantly different properties and biological effects. Christensen summarizes some of the different properties of the types of materials on pages 35 & 36. Christensen's experimental results bear out the differences in the materials. "The biopsies from the inflammatory nodules differed depending on type of injected filler." Christensen at p. 38, left column. Moreover, Christensen specifically addresses the distinction between homogeneous gels and microparticles. Studies show "a higher production of connective tissue in gels with microsphere or fragments than in homogenous gels." Christensen at p. 44, right column. Also, "homogeneous gels ... elicit a minimal host response," while "combination gels," which contain microspheres, "produce a strong host response." Christensen at p. 44, left column. Christensen demonstrates, therefore, that homogeneous gels have very different biological effects as compared to solid microparticle gels.

(10) Vogel discloses the use of derivatives of acrylamide rather than "combining acrylamide and methylene bis-acrylamide." Vogel discloses using methylolacrylamide or methylacrylamide derivatives (Examples 6.1 and 6.2) and dimethylacrylamide and a dimethylmethacrylacrylate derivative (Example 6.3). Likewise, the patents referenced by Vogel, U.S. Patent No. 5,648,100 and France Patent No. 2,378,808, do not disclose the combination of "acrylamide and methylene bis-acrylamide." Vogel at column 8, lines 37-39. Vogel does mention myriad potential monomers, including acrylamide as a potential monomer and methylene bis-acrylamide as potential difunctional monomer. Vogel at column 7, lines 16-21. Yet one of

skill in the art would have no reason to select these two from all possible combinations. In fact, the failure to disclose the combination of the two suggests that Vogel considered the combination unsuitable for its intended purpose. Accordingly, Vogel would not suggest to one of skill in the art "combining acrylamide and methylene bis-acrylamide."

(11) Vogel's microparticles also must be cationic. That is, the microparticles must carry a positive charge. Specifically, Vogel states that the "microparticles preferably contain a positive charge on their surface by way of a cationic monomer or polymer" (Vogel at column 4, lines 36-28), and in the case of treatment of urinary incontinence, the microparticles must contain, among other things, "a positive charge" (Vogel at column 4, line 56). Vogel is replete with teachings that the microparticles must be positively charged. *See, e.g.*, Vogel at column 5, line 41, column 6, lines 65-66. The polymer defined by the pending claims, however, is not cationic.[1]

(12) Vogel also does not teach or suggest "a hydrogel that comprises about 0.5% to 25% by weight of a polymer." Even if Vogel's microparticles could be considered a hydrogel, which is inconsistent with the use of that term in the art, and even if Vogel's polymer would be considered polyacrylamide, Vogel does not suggest the recited weight percent of polymer. Column 7, lines 6-11, of Vogel discloses an acrylic copolymer that comprises about 25% to about 98% neutral hydrophilic acrylic monomer by weight, about 2% to about 50% difunctional monomer by weight, and about 0% to about 50% by weight of one or more monomers having a cationic charge. Accordingly, this section of Vogel's disclosure relates to microspheres with a minimum solid weight content of about 27% weight percent (25% of the acrylic monomer + 2% of the difunctional monomer = 27%, since conversion is near 100%). However, Example 6.1, Vogel discloses a methylolacrylamide (again, not acrylamide) copolymer where there is approximately 10 g of starting monomers. After the reaction, the rigid product is cut, washed and sieved. Washing and sieving lowers and then increases, respectively, the solid weight content of the polymer, and the solid weight content of the polymer is not disclosed nor can it be calculated. Because Vogel's minimum solid content is either greater than the maximum recited by the claims or is not otherwise

[1] Crosslinking could create some cationic or anionic moieties, but any of these moieties would be extremely rare. Accordingly, a skilled person in the field would not consider a polymer cationic or anionic simply because it has some of these chance anionic or cationic moieties.

determinable, Vogel does not teach the recited polymer content, even if Vogel disclosed a hydrogel, or disclosed polyacrylamide.

(13) Vogel also does not suggest a polymer that is "a product of a method comprising combining acrylamide and methylene bis-acrylamide in a molar ratio of 150:1 to 1000:1." Vogel states that its microparticles can comprise an acrylic copolymer that comprises about 25% to about 98% neutral hydrophilic acrylic monomer by weight, about 2% to about 50% difunctional monomer by weight, and about 0% to about 50% by weight of one or more monomers having a cationic charge. Vogel at col. 7, ll. 6-11. In a preferred embodiment, Vogel discloses a copolymer comprising about 25-98% methacrylamide by weight, and about 2-50% N,N-methylene-bis-acrylamide by weight. Vogel at col. 7, ll. 28-31.

(14) The Examiner is correct that the percents of monomer can be converted to molar ratios. Specifically, the percent monomer values can be converted to molar ratios based on the molecular weights of the different monomers, which are provided in APPENDICES 2 and 3.[2] Assuming 100 g of polymer, 25 wt% acrylamide and 50 wt% bis-acrylamide results in 0.352 moles acrylamide and 0.324 moles bisacrylamide:

- (25 g acrylamide)/(71.1 g/mole) = 0.352 moles acrylamide
- (50 g bis-acrylamide)/(154.2 g/mole) = 0.324 moles bisacrylamide

Thus, the acrylamide:bis-acrylamide molar ratio is about 1.1:1. Again, assuming 100 g of polymer, 98 wt% acrylamide and 2 wt% bis-acrylamide results in 1.38 moles acrylamide and 0.0130 moles bis-acrylamide:

- (98 g acrylamide)/(71.1 g/mole) = 1.38 moles acrylamide
- (2 g bis-acrylamide)/(154.2 g/mole) = 0.0130 moles bis-acrylamide

[2] These calculations assume that the polymerization reaction proceeds to completion or near-completion. I understand that the examiner makes the assumption that the polymerization reaction does proceed to completion or near-completion. *See* Office Action, at page 5, lines 12-15. Even if this assumption is not accurate, and the weight percentages (wt%) of acrylamide and bis-acrylamide monomers in the copolymers of Vogel do not reflect the weight percentages of the acrylamide and bis-acrylamide starting materials, the numbers are very likely close and would not have a drastic effect on the molar ratios. Moreover, Example 6.1 clearly illustrates a polyacrylamide derivative gel falling outside the scope of the present claims, as discussed below.

Thus, the acrylamide:bis-acrylamide molar ratio is about 106:1. These acrylamide:bis-acrylamide molar ratios ranging from about 1.1:1 to about 106:1 result in a polymer far different than the recited polymer that results from acrylamide:bis-acrylamide molar ratios of 150:1 to 1000:1.

(15) Vogel's Example 6.1, the only one describing preparation of an acrylamide hydrogel, confirms that Vogel's copolymers have molar ratios falling far outside the recited range. In Example 6.1, 90 g of methylolacrylamide monomer and 2 g of methacrylamidopropyl-trimethyl-ammonium-chloride hydrochloride monomer are combined with 10 g of N,N'-methylene-bis-acrylamide difunctional monomer. This yields an acrylamide derivative copolymer comprising about 88.2% by weight methylolacrylamide (90 g methylolacrylamide/102 g total acrylamide) and about 9.8% by weight bis-acrylamide (10 g bis-acrylamide /102 g total acrylamide), values within the preferred monomer weight percentage ranges disclosed by Vogel. This corresponds to a 0.89 moles of methylolacrylamide[3] and 0.065 moles N,N'-methylene-bis-acrylamide.[4] Thus, the molar ratio of methylolacrylamide:bis-acrylamide in the copolymer of Example 6.1 is 14:1 – a value over ten-fold less than the minimum acrylamide:bis-acrylamide molar ratio recited by the claims, 150:1. This results in a polymer that is much "harder" and solid than the recited polymer. The hardness of Vogel's product makes it possible to fractionate it by sieving. Because of the increased molar ratio, Vogel's microparticles would not have a complex viscosity recited by the claims.

(16) The "complex viscosity" and "elasticity modulus" recited by the pending claims are not inherent in Vogel's polymers for reasons that I have already touched on. Specifically, Vogel's polymers have a very different composition than the recited polymers. Because of this difference in composition, one of skill in the field would expect the Vogel's polymers to have a complex viscosity and elasticity modulus very different from the recited ranges. Vogel's polymers would generally be expected to be more rigid and, therefore, more viscous and with a higher elasticity modulus, as compared to the recited polymer.

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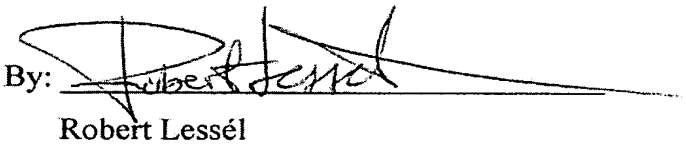
[3] Calculated using a molecular weight of 101.1 g/mol: (90 g methylolacrylamide) / (101.1 g methylolacrylamide /mole) = 0.89 moles

[4] Calculated using a molecular weight of 154.2 g/mol: (10 g N,N'-methylene-bis-acrylamide) / (154.2 g N,N'-methylene-bis-acrylamide/mole) = 0.065 moles

(17) Because of the great differences between Vogel's microparticles and the recited hydrogel, one of ordinary skill in the field would not consider the recited polymer obvious in view of Vogel. The materials differ in type (hydrogel v. particulated microparticles), content of polymer, chemical composition, molar ratio, complex viscosity, and elasticity modulus. Because of the differences in structure and composition, Vogel's polymers would have far different properties than the recited polymer. Accordingly, one of skill in the field would have to diverge greatly from Vogel to obtain the recited polymers. A person knowledgeable of the field would not consider this departure from Vogel to be obvious, and certainly would not reasonably expect to obtain a polymer suitable for the purposes addressed by Vogel.

(18) I further declare that all the statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements are so made punishable by fine or imprisonment, or both, under Section 101 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 19 Oct 2009

By: 

Robert Lessél

APPENDIX 1

CURRICULUM VITAE

Name:	Robert Lessèl.
Nationality:	Danish.
Address:	Bryggerdammen 21, 2605 Brøndby, Denmark.
Telephone:	3675-8830.
Born:	6. august 1963 in Glostrup, Copenhagen.
Personal status:	Married, 3 children age 8, 14 and 17.
Education:	1982: Graduated high school, Statsgymnasiet Schneekloths skole 1988: M. Sc.(Eng.), Chemical Engineer, Technical University of Denmark, specialized in polymer chemistry. Examination work: Modification of polymeric membranes and Phenyl substituted aromatic liquid crystalline polymers. 1989: Patent Examiner at The Danish Patent Office. 1996: Examined as Project Manager, ETM, IHB-Denmark. 2003: Introduction to Management, Right Kjaer & Kjerulf.
Employments:	October 1988 - December 1990 Patent Examiner at The Danish Patent Office within the area "Phosphoric Compounds and polymers". January 1991- ...: Project Manager and Consulting Engineer within polymeric chemistry & processing at Chempilots a/s (previously Wolff & Kaaber A/S). Chempilots work has included: Independent problem-solving, preparation of experimental plans, experiments in the laboratory and at the client, reporting and follow up. Internal/external collaboration with scientific and technical staff including direct

customer contacts with several Danish and International companies, mainly from the Medical Device industry.

Examples of major Projects:

1991: "Development of effective resin composites as substitute for amalgam", performed in association with Dr. Odont E.C.Munksgaard, Dental School, Copenhagen.
The project is supported by the Danish Environmental Protection Agency.

1994-2000: MUP II program: "Stability and strength of the bonds between polymers and the inorganic fillers", in association with the Danish company Nordisk Tråd & Kabel A/S (NKT research center) and two state laboratories at H C Ørsteds institute, University of Copenhagen and Risø, Department of Solid state Physics.

1999-2002: Thor program: " Design of new functional polymer composite Materials"; exploration of the use of supercritical CO_2 as solvent in preparation and modification of polymeric based materials.

Optimization of Bone Cement formulation, Polyurethane foam and Controlled Release system. Processing assignments with regards to Casting of plastic Fresnel screens. Synthesis of Polymer based materials used as conducting/medical skin adhesives and ECG, and development and synthesis/ analysis of polymeric based Hydrogel products for use as colorants for soft contact lenses and soft tissue filler.

Handling of patent applications internally and for customers including elaboration of patent applications, forming strategies and drawing up budgets, correspondence with Danish and foreign patent agents.

Supplementary achievements and references:

Participated regularly in national and international congresses, courses, meetings and workshops since 1988 within the scientific areas of Polymer Chemistry and Technology, Synthesis and processing of Polymer based Hydrogels, Characterization and Analysis of Polymeric based materials and Patent related topics.

Training courses in HPLC, Perkin Elmer.

Trained in ISO9001 and GMP for use in laboratory and production.

Trained in literature searching using STN incl. Chemical Abstract.

Taken classes in Taguchi experimental planning and Statistic with Statgraphic, DIEU.

Teaching experience & publications :

1990: Instructor in Patent examination, The Danish Patent Office.

1991: Internal lecture, Topic: Patents - protection of research and development.

1992: Lecture for leading staff at dnp denmark A/S, topic: Polymerization processes in manufacturing of Fresnel screens.

1995: Invited speaker to a meeting arranged by the DSM, a society under The Society of Danish Engineers, topic: Use of polymeric composite materials instead of amalgam.

2004: Invited speaker at the annually meeting in the Society of Processing in Organic Chemistry, Cheminova: Use of Supercritical CO_2 in Organic Chemistry.

2000: Co-inventor on several patent applications regarding polyacrylamide based hydrogels.

1990: M.H.B. Skovby, R. Lessèl and J. Kops, J.: Thermal

properties of Some Fully Aromatic Thermotropic Liquid Crystal Polyesters Polym. Sci. A. Polym. Chem. Ed., 28, 75 (1990)

1990: Article i Patentdirektoratets personaleblad om "Nordiske Polymerdagar 1990", R. Lessèl, 9/1990.

1992-1998: Munksgaard, EC, Wolff & Kaaber A/S: Erstatningsmaterialer for sølvamalgam, Arbejdsrapport, Miljøstyrelsen 1992, 1994, 1997 og 1998

1996: Artikel i Tandlægebladet: Plastfyldninger i støbeskeen, 100, 1996, s. 190 -191

1997: Interview til Materiale & Muligheder: Ny viden om avanceret plast.

1998: Munksgaard, EC, Wolff & Kaaber A/S: Erstatningsmaterialer for Amalgam til tandfyldninger, Projektrapport, Miljøstyrelsen 1998

1997: Lessèl, R; Elbek, C: Rheological Characterization of highly filled dental restorative composite in the uncured state; Poster at Nordic Polymer Days, Lund.

2000: Egsgaard, H; Batsberg, W; Møllgaard, M; Lessèl, R; Glastrup, J: Mass spectrometry of Polyethylene Glycols; Proceeding and poster at International MS meeting in Barcelona.

Schaumburg, K; Jespersen, H.T; Khokhlov, A; Karthäuser, J; Lessèl, R: Kemi i superkritisk CO_2; dansk kemi, 84, nr. 11, s. 26 – 30.

Memberships:

1990: Member of the Advisory committee on the project "Development of effective resin composites as substitute for amalgam", appointed by the Danish Environmental Protection Agency.

1999-2002: Member of the Steering group FUCOMA in the public financed THOR project " Design of new functional polymer composite materials".

2008- : Member of the board of the Danish Society for Polymer Technology under the Danish Society of Engineers, IDA.

APPENDIX 2

3050 Spruce Street
Saint Louis, Missouri 63103 USA
Telephone (800) 325-5832 (314) 771-5765
Fax (314) 286-7828
email: techserv@sial.com
sigma-aldrich.com

ProductInformation

ACRYLAMIDE
MOLECULAR BIOLOGY REAGENT
Sigma Prod. No. A 9099

STRUCTURE: CH_2=CH-CO-NH_2
CAS NUMBER: 79-06-1
SYNONYM: 2-propenamide

Product Description
Appearance: White powder
Molecular formula: C_3H_5NO
Molecular weight: 71.08
Melting point: 84.5 °C, although stable in the dark, it readily polymerizes at its melting point, in solution or under ultraviolet light.[1]
Special tests: DNase, RNase and Protease were not detected per procedures on lot-specific data sheet.

Acrylamide as a monomer is used in a variety of synthetic processes to form polymers, copolymers. It is readily polymerized in the presence of free radicals, usually in aqueous solutions. Polyacrylamide plastics have numerous commercial applications, due in part to the tendency of polyacrylamide to adsorb many times its own mass in water.

In biochemistry, its principle use is in the preparation of polyacrylamide gels, using suitable cross-linkage agents, for use in electrophoresis separation techniques. Common reaction initiators are riboflavin, ammonium persulfate; varying the ratio of acrylamide to crosslinking agent permits the formation of a gel with predictable average pore size and texture. A number of excellent laboratory manuals give specific protocols for preparing "PAGE" (Polyacrylamide Gel Electrophoresis) gels; see page 2 for a partial reference list. Acrylamide has a tendency to hydrolyze under acidic or basic conditions to form acrylic acid.

Acrylic acid and any ionic impurities in the acrylamide can have significant effects on the performance of the PAGE gel formed, since the voltage across the gel is affected by the ionic charge of the gel and usage buffers. Sigma tests each lot of A9099 for its suitability for use in electrophoresis of nucleic acids (more detail is available on lot-specific information sheets sent with the product.) Several other products are also available: A 3553, Electrophoresis Reagent, which has a higher purity specification and additional testing for trace impurities, solution conductivity and acrylic acid content; and A 4058, which is a ready-to-use 40% solution prepared from A 3553; A8887 is also of high purity, but has not received as extensive testing for application suitability.

NOTE:
Acrylamide as a monomer is considered toxic, directly affecting the nervous system, and it may reasonably be considered to be a carcinogen.[4] Acrylamide is readily absorbed through intact skin from aqueous solutions.[1] Please consult the Material Safety Data Sheet and appropriate safety procedures before handling this material. Once polymerized, the solid POLYacrylamide is considered quite safe, although PAGE gels should still be handled with gloves under the assumption that they may still contain unreacted monomer.

Storage/Stability
If acrylamide is kept protected from light, it is expected to be stable indefinitely at room temperature. After three weeks storage at 50 °C, there is no evidence of polymer formation and only slight yellowing occurs. Even after 24 hours at 80 °C (slightly below melting), pure samples show little or no polymer formation.[3] It should be evaluated for continued suitability every three years.

Acrylamide is routinely tested at 250 mg/mL in water, giving a clear colorless solution. It is soluble at least to 40% (w/v) in water[2], and reportedly up to 215 g/100 mL in water at 30 °C.[1] It is soluble in methanol (155 g/100 mL), ethanol (86 g/100 mL), acetone (63.1 g/100 mL); only minimally soluble in benzene or heptane.[1]

Solutions should be stable at 2-8 °C for at least a year if stored protected from light.[2]

References

1. *Merck Index*, 12th Ed., #131 (1996).
2. Sigma data.
3. Supplier information.
4. Sigma Material Safety Data Sheet.

Additional Usage References:

1. *Protein Structure: A Practical Approach*, ed. T.E. Creighton (IRL PRESS, 1990), pages: 4-8, 36-38, 523-55, 79-80, 150-151, 233-234.
2. *Gel Electrophoresis: Essential Data*, D. Patel (Wiley Press, 1994) - A small book with extensive recipes for gel production.
3. *Gel Electrophoresis of Proteins: A Practical Approach*, 2nd Ed., eds. B.D. Hames and D. Rickwood (IRL Press, 1994)
4. *Electrophoresis: Theory, Techniques, and Biochemical and Clinical Applications*, 2nd Ed., A.T. Andrews (Oxford University Press, 1986).

JWM 5/29/2003

Material Safety Data Sheet
Bis-Acrylamide

ACC# 16077

Section 1 - Chemical Product and Company Identification

MSDS Name: Bis-Acrylamide
Catalog Numbers: AC163800000, AC163800050, AC163801000, AC163805000, AC164790000, AC164795000, 16479-0250, 16479-1000, BP171-100, BP171-25
Synonyms: N,N'-Methylenebis(acrylamide); N,N'-Methylenebis(2-propenamide); Methylenediacrylamide; Methylenebisacrylamide; MBA; Bisacrylamide; BAC; cross-linking agent.
Company Identification:

Fisher Scientific
1 Reagent Lane
Fair Lawn, NJ 07410

For information, call: 201-796-7100
Emergency Number: 201-796-7100
For CHEMTREC assistance, call: 800-424-9300
For International CHEMTREC assistance, call: 703-527-3887

Section 2 - Composition, Information on Ingredients

CAS#	Chemical Name	Percent	EINECS/ELINCS
110-26-9	N,N'-Methylenebis(acrylamide)	>95	203-750-9

Section 3 - Hazards Identification

EMERGENCY OVERVIEW

Appearance: white solid.
Warning! Harmful if swallowed. Causes eye, skin, and respiratory tract irritation. May be harmful if absorbed through skin or if inhaled. May cause nervous system effects. Light sensitive. Refrigerate upon arrival below 4°C/39°F. May cause adverse reproductive effects based upon animal studies.
Target Organs: Eyes, nervous system, reproductive system, skin.

Potential Health Effects
Eye: Causes eye irritation.
Skin: Causes skin irritation. May be absorbed through the skin.
Ingestion: Harmful if swallowed. May cause irritation of the digestive tract. Like acrylamide, may cause central, peripheral, and autonomic nervous system effects.
Inhalation: Causes respiratory tract irritation. Acrylamide, a similar compound, can be absorbed through the lungs and overexposure will produce signs of neurotoxicity. Inhalation studies with methylenebisacrylamide have produced acute pulmonary edema in animals.
Chronic: Adverse reproductive effects have been reported in animals. Prolonged or repeated exposure affects the nervous system.

Section 4 - First Aid Measures

Eyes: In case of contact, immediately flush eyes with plenty of water for a t least 15 minutes. Get medical aid.
Skin: In case of contact, flush skin with plenty of water. Remove contaminated clothing and shoes. Get medical aid if irritation develops and persists. Wash clothing before reuse.
Ingestion: If swallowed, do not induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. Get medical aid.
Inhalation: If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical aid.
Notes to Physician: Treat symptomatically and supportively.
Antidote: Pyridoxine (vitamin B6), pyruvate, and N-acetylcysteine have been used to reduce the toxicity of acrylamide in experimental studies, but are unproven.

Section 5 - Fire Fighting Measures

General Information: As in any fire, wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. Combustion generates toxic fumes. Use water spray to keep fire-exposed containers cool. This material in sufficient quantity and reduced particle size is capable of creating a dust explosion. Approach fire from upwind to avoid hazardous vapors and toxic decomposition products.
Extinguishing Media: Use water spray, dry chemical, carbon dioxide, or chemical foam.
Flash Point: Not applicable.
Autoignition Temperature: Not applicable.
Explosion Limits, Lower: Not available.
Upper: Not available.
NFPA Rating: (estimated) Health: 2; Flammability: 1; Instability: 1

Section 6 - Accidental Release Measures

General Information: Use proper personal protective equipment as indicated in Section 8.
Spills/Leaks: Vacuum or sweep up material and place into a suitable disposal container. Avoid generating dusty conditions. Provide ventilation.

Section 7 - Handling and Storage

Handling: Wash thoroughly after handling. Remove contaminated clothing and wash before reuse. Use with adequate ventilation. Minimize dust generation and accumulation. Avoid contact with eyes, skin, and clothing. Avoid breathing dust.
Storage: Store in a tightly closed container. Keep refrigerated. (Store below 4°C/39°F.) Keep away from polymerization catalysts. Store away from heat, oxidizing agents, acids, alkalies, and sunlight.

Section 8 - Exposure Controls, Personal Protection

Engineering Controls: Facilities storing or utilizing this material should be equipped with an eyewash facility and a safety shower. Use adequate ventilation to keep airborne concentrations low.

Exposure Limits

Chemical Name	ACGIH	NIOSH	OSHA - Final PELs
N,N'-Methylenebis (acrylamide)	none listed	none listed	none listed

OSHA Vacated PELs: N,N'-Methylenebis(acrylamide): No OSHA Vacated PELs are listed for this chemical.

Personal Protective Equipment

Eyes: Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin: Wear appropriate protective gloves to prevent skin exposure.

Clothing: Wear appropriate protective clothing to prevent skin exposure.

Respirators: Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Section 9 - Physical and Chemical Properties

Physical State: Solid
Appearance: white
Odor: none reported
pH: >5 (2.5% soln)
Vapor Pressure: Negligible.
Vapor Density: 5.31 (air=1)
Evaporation Rate: Negligible.
Viscosity: Not available.
Boiling Point: Not available.
Freezing/Melting Point:> 300 deg C
Decomposition Temperature: Not available.
Solubility: Slightly soluble.
Specific Gravity/Density:1.2 (water=1)
Molecular Formula:C7H10N2O2
Molecular Weight:154.17

Section 10 - Stability and Reactivity

Chemical Stability: Stable. However, may decompose if heated. May polymerize on exposure to light.

Conditions to Avoid: Light, heat.

Incompatibilities with Other Materials: Strong oxidizing agents, strong reducing agents, strong acids, strong bases.

Hazardous Decomposition Products: Carbon monoxide, oxides of nitrogen, carbon dioxide, ammonia and/or derivatives.

Hazardous Polymerization: May occur.

Section 11 - Toxicological Information

RTECS#:
CAS# 110-26-9: AS3678000
LD50/LC50:
CAS# 110-26-9:
Oral, mouse: LD50 = 380 mg/kg;
Oral, rat: LD50 = 390 mg/kg;

Carcinogenicity:
CAS# 110-26-9: Not listed by ACGIH, IARC, NTP, or CA Prop 65.

Epidemiology: No information available.
Teratogenicity: Administration of BAC by gavage to pregnant mice produced an increase in skeletal variations among fetuses at maternal doses of 10 mg/kg/d. Maternal toxicity was not encountered below 30 mg/kg/d.
Reproductive Effects: Methylenebisacrylamide (MBA) was found to have greater testicular effects than detectable neurotoxic effects in mice. MBA showed dominant lethal reproductive toxicity in F0 males (fewer live pups/litter, more resorptions) and females (lowered F1 pupweight) at exposure levels that did not affect body weight and had no effect on grip strength or histopathologic measures of neurotoxicity.
Mutagenicity: See actual entry in RTECS for complete information.
Neurotoxicity: Neurotoxic effects have occurred in experimental animals.
Other Studies:

Section 12 - Ecological Information

No information available.

Section 13 - Disposal Considerations

Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. US EPA guidelines for the classification determination are listed in 40 CFR Parts 261.3. Additionally, waste generators must consult state and local hazardous waste regulations to ensure complete and accurate classification.
RCRA P-Series: None listed.
RCRA U-Series: None listed.

Section 14 - Transport Information

	US DOT	Canada TDG
Shipping Name:	Not Regulated	Not Regulated
Hazard Class:		
UN Number:		
Packing Group:		

Section 15 - Regulatory Information

US FEDERAL

TSCA
CAS# 110-26-9 is listed on the TSCA inventory.
Health & Safety Reporting List
None of the chemicals are on the Health & Safety Reporting List.
Chemical Test Rules
None of the chemicals in this product are under a Chemical Test Rule.
Section 12b
None of the chemicals are listed under TSCA Section 12b.
TSCA Significant New Use Rule
None of the chemicals in this material have a SNUR under TSCA.
CERCLA Hazardous Substances and corresponding RQs
None of the chemicals in this material have an RQ.
SARA Section 302 Extremely Hazardous Substances
None of the chemicals in this product have a TPQ.
SARA Codes
CAS # 110-26-9: immediate, delayed, reactive.
Section 313 No chemicals are reportable under Section 313.
Clean Air Act:
This material does not contain any hazardous air pollutants.
This material does not contain any Class 1 Ozone depletors.
This material does not contain any Class 2 Ozone depletors.
Clean Water Act:
None of the chemicals in this product are listed as Hazardous Substances under the CWA.
None of the chemicals in this product are listed as Priority Pollutants under the CWA.
None of the chemicals in this product are listed as Toxic Pollutants under the CWA.
OSHA:
None of the chemicals in this product are considered highly hazardous by OSHA.
STATE
CAS# 110-26-9 is not present on state lists from CA, PA, MN, MA, FL, or NJ.

California Prop 65

California No Significant Risk Level: None of the chemicals in this product are listed.

European/International Regulations

European Labeling in Accordance with EC Directives
Hazard Symbols:
XN
Risk Phrases:
R 20/21/22 Harmful by inhalation, in contact with skin and if swallowed.
R 36/37/38 Irritating to eyes, respiratory system and skin.

Safety Phrases:
S 26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S 36/37 Wear suitable protective clothing and gloves.

WGK (Water Danger/Protection)
CAS# 110-26-9: 2

Canada - DSL/NDSL

CAS# 110-26-9 is listed on Canada's DSL List.

Canada - WHMIS

not available.

This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations and the MSDS contains all of the information required by those regulations.

Canadian Ingredient Disclosure List

Section 16 - Additional Information

MSDS Creation Date: 12/12/1997
Revision #11 Date: 11/08/2007

APPENDIX 3

MATERIAL SAFETY DATA SHEET

Date Printed: 07/27/2009
Date Updated: 01/28/2006
Version 1.4

Section 1 - Product and Company Information

Product Name	N-(HYDROXYMETHYL)ACRYLAMIDE, 48 WT. % SOLUTION IN WATER
Product Number	245801
Brand	ALDRICH
Company	Sigma-Aldrich
Address	3050 Spruce Street SAINT LOUIS MO 63103 US
Technical Phone:	800-325-5832
Fax:	800-325-5052
Emergency Phone:	314-776-6555

Section 2 - Composition/Information on Ingredient

Substance Name	CAS #	SARA 313
N-(HYDROXYMETHYL)ACRYLAMIDE SOLUTION	None	Yes

Ingredient Name	CAS #	Percent	SARA 313
WATER	7732-18-5	52	No
N-(HYDROXYMETHYL)ACRYLAMIDE	924-42-5	48	Yes
4-METHOXYPHENOL	150-76-5	< 0.01	No

Formula C4H7NO2

Section 3 - Hazards Identification

EMERGENCY OVERVIEW

Toxic (USA) Harmful (EU).
Harmful if swallowed. Irritating to eyes, respiratory system and skin.
Target organ(s): Liver. Lungs. Readily absorbed through skin.

HMIS RATING

HEALTH: 2*
FLAMMABILITY: 0
REACTIVITY: 1

NFPA RATING

HEALTH: 2
FLAMMABILITY: 0
REACTIVITY: 1

*additional chronic hazards present.

For additional information on toxicity, please refer to Section 11.

Section 4 - First Aid Measures

ORAL EXPOSURE

If swallowed, wash out mouth with water provided person is

conscious. Call a physician.

INHALATION EXPOSURE
If inhaled, remove to fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen.

DERMAL EXPOSURE
In case of skin contact, flush with copious amounts of water for at least 15 minutes. Remove contaminated clothing and shoes. Call a physician.

EYE EXPOSURE
In case of contact with eyes, flush with copious amounts of water for at least 15 minutes. Assure adequate flushing by separating the eyelids with fingers. Call a physician.

Section 5 - Fire Fighting Measures

FLASH POINT
N/A

AUTOIGNITION TEMP
N/A

FLAMMABILITY
N/A

EXTINGUISHING MEDIA
Suitable: Water spray. Carbon dioxide, dry chemical powder, or appropriate foam.

FIREFIGHTING
Protective Equipment: Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.
Specific Hazard(s): Emits toxic fumes under fire conditions.

Section 6 - Accidental Release Measures

PROCEDURE TO BE FOLLOWED IN CASE OF LEAK OR SPILL
Evacuate area.

PROCEDURE(S) OF PERSONAL PRECAUTION(S)
Wear self-contained breathing apparatus, rubber boots, and heavy rubber gloves.

METHODS FOR CLEANING UP
Cover with dry lime or soda ash, pick up, keep in a closed container, and hold for waste disposal. Ventilate area and wash spill site after material pickup is complete.

Section 7 - Handling and Storage

HANDLING
User Exposure: Do not breathe vapor. Avoid contact with eyes, skin, and clothing. Avoid prolonged or repeated exposure.

STORAGE
Suitable: Keep tightly closed.

SPECIAL REQUIREMENTS
Light sensitive.

Section 8 - Exposure Controls / PPE

ENGINEERING CONTROLS
Use only in a chemical fume hood. Safety shower and eye bath.

PERSONAL PROTECTIVE EQUIPMENT
Respiratory: Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU). Where risk assessment shows air-purifying respirators are appropriate use a full-face respirator with multi-purpose combination (US) or type ABEK (EN 14387) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator.
Hand: Compatible chemical-resistant gloves.
Eye: Chemical safety goggles.

GENERAL HYGIENE MEASURES
Wash thoroughly after handling.

Section 9 - Physical/Chemical Properties

Appearance Physical State: Liquid

Property	Value	At Temperature or Pressure
Molecular Weight	101.1 AMU	
pH	N/A	
BP/BP Range	N/A	
MP/MP Range	N/A	
Freezing Point	N/A	
Vapor Pressure	N/A	
Vapor Density	N/A	
Saturated Vapor Conc.	N/A	
Bulk Density	N/A	
Odor Threshold	N/A	
Volatile%	N/A	
VOC Content	N/A	
Water Content	N/A	
Solvent Content	N/A	
Evaporation Rate	N/A	
Viscosity	N/A	
Surface Tension	N/A	
Partition Coefficient	N/A	
Decomposition Temp.	N/A	
Flash Point	N/A	
Explosion Limits	N/A	
Flammability	N/A	
Autoignition Temp	N/A	
Refractive Index	N/A	
Optical Rotation	N/A	
Miscellaneous Data	N/A	
Solubility	N/A	

N/A = not available

Section 10 - Stability and Reactivity

STABILITY
Stable: Stable.
Conditions to Avoid: May polymerize on exposure to light.
Materials to Avoid: Strong oxidizing agents.

HAZARDOUS DECOMPOSITION PRODUCTS
Hazardous Decomposition Products: Carbon monoxide, Carbon dioxide, Nitrogen oxides.

HAZARDOUS POLYMERIZATION
Hazardous Polymerization: Will not occur

Section 11 - Toxicological Information

ROUTE OF EXPOSURE
Skin Contact: Causes skin irritation.
Skin Absorption: May be harmful if absorbed through the skin.
Eye Contact: Causes eye irritation.
Inhalation: Material is irritating to mucous membranes and upper respiratory tract. May be harmful if inhaled.
Ingestion: Harmful if swallowed.

TARGET ORGAN(S) OR SYSTEM(S)
Lungs. Liver.

SIGNS AND SYMPTOMS OF EXPOSURE
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

CHRONIC EXPOSURE - CARCINOGEN
Result: This product is or contains a component that is not classifiable as to its carcinogenicity based on its IARC, ACGIH, NTP, or EPA classification.

Section 12 - Ecological Information

No data available.

Section 13 - Disposal Considerations

APPROPRIATE METHOD OF DISPOSAL OF SUBSTANCE OR PREPARATION
Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Observe all federal, state, and local environmental regulations.

Section 14 - Transport Information

DOT
Proper Shipping Name: None
Non-Hazardous for Transport: This substance is considered to be non-hazardous for transport.

IATA
Non-Hazardous for Air Transport: Non-hazardous for air transport.

Section 15 - Regulatory Information

EU ADDITIONAL CLASSIFICATION
Symbol of Danger: Xn
Indication of Danger: Harmful.
R: 22-36/37/38
Risk Statements: Harmful if swallowed. Irritating to eyes, respiratory system and skin.
S: 26

Safety Statements: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

US CLASSIFICATION AND LABEL TEXT
Indication of Danger: Toxic (USA) Harmful (EU).
Risk Statements: Harmful if swallowed. Irritating to eyes, respiratory system and skin.
Safety Statements: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable protective clothing, gloves, and eye/face protection. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
US Statements: Target organ(s): Liver. Lungs. Readily absorbed through skin.

UNITED STATES REGULATORY INFORMATION
SARA LISTED: Yes
NOTES: This product is or contains a component that is subject to SARA313 reporting requirements.

UNITED STATES - STATE REGULATORY INFORMATION

CALIFORNIA PROP - 65
California Prop - 65: This product is or contains chemical(s) known to the state of California to cause cancer.

CANADA REGULATORY INFORMATION
WHMIS Classification: This product has been classified in accordance with the hazard criteria of the CPR, and the MSDS contains all the information required by the CPR.
DSL: No
NDSL: No

Section 16 - Other Information

DISCLAIMER
For R&D use only. Not for drug, household or other uses.

WARRANTY
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Inc., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale.